S1 Appendix.

Resampling Approach to Obtain the P-value of the Localized Test for Variant \( m \).

1. Expressing the score test statistic \( T_{m,c} \) in terms of the influence function.

Recall that the local kernel score test statistic in POINT for variant \( m \) with a fixed \( c \) is

\[
T_{m,c} = \frac{1}{n} (\hat{e}_1, \ldots, \hat{e}_n)^T K_{m,c}(\hat{e}_1, \ldots, \hat{e}_n),
\]

where \( \hat{e}_i = Y_i - g^{-1}(X_i^T \hat{\beta}) \) is the fitted residual from the KM model under the null hypothesis of no genetic effect. Let \( K_{m,c} = Z_{m,c}Z_{m,c}^T \) and \( [Z_{m,c}^{(i)}]_1 \) be the row vector of \( Z_{m,c} \). Then

\[
T_{m,c} = \frac{1}{n} (\hat{e}_1, \ldots, \hat{e}_n) Z_{m,c} Z_{m,c}^T (\hat{e}_1, \ldots, \hat{e}_n)^T = \left[ \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \hat{e}_i \right] \left[ \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \hat{e}_i \right]^T
\]

By Taylor expansion around the true value of \( \beta \) under the null, denoted by \( \beta_* \), we have

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \hat{e}_i = \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \epsilon_i + \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \frac{\partial \epsilon_i}{\partial \beta^T} (\hat{\beta} - \beta_*) + o_p(1) \tag{1}
\]

where \( \epsilon_i = Y_i - g^{-1}(X_i^T \beta_*) \).

For quantitative traits, Equation (1) becomes

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \hat{e}_i = \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \epsilon_i - \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} X_i^T \sqrt{n} (\hat{\beta} - \beta_*) + o_p(1)
\]

\[
= \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} \epsilon_i - \left( \frac{1}{\sqrt{n}} \sum_{i=1}^n Z_{m,c}^{(i)} X_i^T \right) \left( \frac{1}{\sqrt{n}} \sum_{i=1}^n X_i X_i^T \right)^{-1} \times
\]

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^n X_i (y_i - X_i^T \beta_*) + o_p(1)
\]

\[
= \frac{1}{\sqrt{n}} \sum_{i=1}^n \{ Z_{m,c}^{(i)} - A_2 A_1^{-1} X_i \} \epsilon_i + o_p(1)
\]

\[
\equiv \frac{1}{\sqrt{n}} \sum_{i=1}^n \psi_i + o_p(1), \tag{2}
\]

where \( A_1 = E(X_i X_i^T) \) and \( A_2 = E(Z_{m,c}^{(i)} X_i^T) \). Here \( \psi_i = \{ Z_{m,c}^{(i)} - A_2 A_1^{-1} X_i \} \epsilon_i \) is an influence function that can be consistently estimated by \( \hat{\psi}_i = \{ \hat{Z}_{m,c}^{(i)} - \hat{A}_2 \hat{A}_1^{-1} X_i \} \epsilon_i \),
where
\[ \hat{A}_1 = \frac{1}{n} \sum_{i=1}^{n} X_i X_i^T \quad \text{and} \quad \hat{A}_2 = \frac{1}{n} \sum_{i=1}^{n} Z_{m,c}^{(i)} X_i^T. \]

Similarly, for binary traits, we have
\[ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} Z_{m,c}^{(i)} \hat{\epsilon}_i = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} Z_{m,c}^{(i)} \left( \frac{e^{X_i^T \beta_*}}{(1 + e^{X_i^T \beta_*})^2} X_i^T \right) \sqrt{n} \left( \hat{\beta} - \beta_* \right) + o_p(1) \]
\[ = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left( Z_{m,c}^{(i)} - A_2 A_1^{-1} X_i \right) \epsilon_i + o_p(1) \equiv \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \psi_i + o_p(1), \]
where
\[ A_1 = \mathbb{E} \left( e^{X_i^T \beta (1 + e^{X_i^T \beta})} X_i X_i^T \right) \quad \text{and} \quad A_2 = \mathbb{E} \left( Z_{m,c}^{(i)} e^{X_i^T \beta (1 + e^{X_i^T \beta})} X_i^T \right). \]

2. Details of the weighted chi-square distribution of \( T_{m,c} \)

By the central limit theorem, we have
\[ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} Z_{m,c}^{(i)} \hat{\epsilon}_i \quad \overset{d}{\sim} \quad N(0, \Sigma_{m,c}), \]
where
\[ \Sigma_{m,c} = \mathbb{E} (\psi_i \psi_i^T) = \mathbb{E} \left[ \left( Z_{m,c}^{(i)} - A_2 A_1^{-1} X_i \right)^2 \right]. \]

To obtain the p-value of \( \min P \) over a grid of \( c \) values.

Recall that for variant \( m \), given a grid of \( c \)’s, \( c = c_1, \ldots, c_L \), we adaptively find the optimal \( c \) by choosing the \( c \) that yields \( \min P = \min \{ P_{m,c_1}, \ldots, P_{m,c_L} \} \). Here we describe the approach to obtain the p-value of \( \min P \) (denoted by \( p_m^* \)) for
ranking the variants. Specifically, given that 
\[ T_{m,c} = \left( \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \psi_i \right)^T \left( \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \psi_i \right) + o_p(1) \]
and \( \hat{\psi}_i \)'s can be consistently estimated by \( \hat{\psi}_i \)'s, we can obtain the p-value of the minP of variant \( m \) by perturbing the estimated influence functions \( \hat{\psi}_i \)'s. That is, we generate \( B \) random vectors of length \( n \): \( O_1, ..., O_B \) from a standard Normal distribution and create \( B \) perturbed test statistics of variant \( m \) for each \( c \) value:

\[ T^{(b)}_{m,c} = \left( \frac{1}{\sqrt{n}} \sum_{i=1}^{n} O_{ib} \hat{\psi}_i \right)^T \left( \frac{1}{\sqrt{n}} \sum_{i=1}^{n} O_{ib} \hat{\psi}_i \right) , b = 1, ..., B \]

These \( T^{(b)}_{m,c} \)'s have to be converted to p-values, denoted as \( p^{(b)}_{m,c} \)'s, e.g., using Davies method so to be comparable across different \( c \) values. We can then calculate the \( b^{th} \) perturbed minP statistic over different \( c \)'s, i.e., \( \min P^{(b)}_m = \min_c \{ p^{(b)}_{m,c} \} , b = 1, ..., B \). Finally, our minP p-value for variant \( m \) is \( p^*_m = \frac{1}{B} \sum_{b=1}^{B} I(\min P^{(b)}_m < \min P_m) \), where \( I(\cdot) \) is the indicator function. These p-values can be used to rank and select promising variants, e.g., to select the top \( J \) variants with \( p^*_m \) less than a certain threshold.